Predicting Optimal Strategies for Microbial Metabolic Pathways

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Summary

Microbes have higher fitness if the specific flux that they require is maximised. This thesis elucidates some aspects of this evolutionary forcing.

In Chapter 2, a five-state model of glycolysis in *S. Cerevisiae* is analysed. This is an extension of the three-state model analysed in [19]. We present a bifurcation that is remarkably simple and we shed light on the influence of NADH on the bistability between the imbalanced state and a regular steady state. Furthermore we show that there is a tradeoff in the level of expression of upper glycolysis for starved yeast cells. The speed of adaptation to a new source of glucose and likelihood of the imbalanced state are both increased with a higher expression. The population can cope by having heterogeneity in the upper-glycolytic expression across the population. A subpopulation will end up in the imbalanced state, but on the whole, the population has optimal adaptation.

In Chapter 3 we present a model of a linear chain of n enzymatic reactions that allocates its enzyme production capacity $\boldsymbol{\varepsilon}$ dynamically. The objective of this allocation is optimal specific flux. The allocation $\boldsymbol{\varepsilon}$ follows the concentration of one metabolite, the sensor x_s. As the sensor indirectly registers change in the external nutrient concentration $\underline{x_0}$, this is a robust design for adaptive control that optimises specific flux. In this chapter we shed light on the quasi steady state (QSS) that follows from timescale separation; we assume that metabolism balances out quickly, while the enzyme production and growth rate are more

slow to adapt. The QSS is a bijection between the metabolite and enzyme concentrations and we prove local stability of the unique optimum. These results and their restrictions are further illustrated through numerical simulation of the smallest possible linear chain.

In Chapter 4 we consider models that are similar to the one in Chapter 3. We consider the relation between the sensor concentration x_s as input and the resulting enzyme production $\boldsymbol{\varepsilon}$. This input output relation is thus a theoretical prediction of robust, adaptive control for optimal specific flux, following the kinetic functions f_j and the stoichiometry.

Chapter 4 is an exploratory work, where the main goal is to understand the input output relations, but without a specific end result in mind. The analysis consists of a theoretical derivation of two limits at the endpoints of the domain for x_s, and numerical simulations to discover trends in these relations.

A number of insights are gained from the analysis in Chapter 4. The equilibrium limit is a neat function of the parameters. Our derivation gives full insight into the parameter sensitivity of the enzyme distribution $\boldsymbol{\varepsilon}$ at this end of the domain for x_s. The other limit sets the nutrient concentration and consequently all internal metabolite concentrations, including the sensor, to infinity. This implies full substrate saturation of all constituent enzymes, from which we show that the enzyme investment is proportional to the time an enzyme takes to convert substrate into product.

Apart from this limiting behaviour, we consider these functions of the sensor x_s in numerical simulations. Here we see that the orientation of the two limits of the domain for x_s provides a strong indication of its increasing or decreasing tendency: if the limit at equilibrium is lower than the limit at infinity the function will be increasing and vice versa. However, the functions can also be non-monotone. Furthermore the presence of multiple nutrients, the sensitivity of internal concentrations to the nutrient in optimum, and scalability are researched for trends with numerical simulations. In this way, we can predict the input output relation better.